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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,379	SWANSON ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 11, 2009. Currently, claims 1-5 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. This action is FINAL.

4. Any objections and rejections not reiterated below are hereby withdrawn.

   a. In view of the addition of the priority claim to the specification, the 102(a) rejection has been withdrawn.

   b. In view of the amendment to the claims to require a particular polymorphism, the written description rejection has been withdrawn.

Election/Restrictions

5. Applicant's election without traverse of Group 1, Claims 1-6 in the paper filed May 22, 2007 is acknowledged.

6. In the election filed May 11, 2009, applicant elected a A polymorphism of the A-C SNP in DRD4 intron 3.

The requirement is still deemed proper and is therefore made FINAL.

Priority

7. This application claims priority to provisional application 60/433,045, filed December 13, 2002.

Claim Objections

8. Claim 1 is objected to because of the following informalities: 1(b) uses SCP. It is presumed this should read "SNP". Appropriate correction is required.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working

examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method of testing a patient for ADHD by testing for a marker in linkage disequilibrium surrounding the DRD4 7R allele, wherein the marker is an A polymorphism of the A-C SNP pair in DRD4 intron 3 and evaluating the level of dopamine release.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the art

The art teaches girls and boys respond differently to the effects of exercise on children with ADHD. Tantillo et al. (Medicine and Science in Sports & Exercise, 2002, pages 203-212). Tantillo teaches that the boys and girls had different reactions to exercise with ADHD. The findings suggest an interaction between sex and exercise intensity that is not explained by physical fitness. Thus, it is unpredictable that girls and boys experience the same levels and response to stimulus.

The art analyzes 103 individuals and identifies 70 SNPs/polymorphisms (see Wang et al. Am. J. Hum. Genetics, Vol. 74, pages 931-944, 2004). Table 1, as provided in Wang, provides a few exemplary polymorphisms. Of these polymorphisms, Wang specifically marks a few of the SNPs, deletions and repeats as highly linked to the 7R allele (see Table 1). The instant specification fails to provide any description of these polymorphisms and the three polymorphisms within the specification are not representative of these polymorphisms.

Similarly, Bhaduri teaches association of DRD4 polymorphisms with ADHD in Indian population. Bhaduri finds the exon 1 12bp duplication and exon 3 48pb VNTR in strong disequilibrium. However, Bhaduri teaches the alleles of 12bp duplication are not associated with ADHD. Thus, there is no description of markers surrounding the DRD4 7R allele which are within linkage disequilibrium and are associated with ADHD.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that

each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the full scope of the claimed invention may be practiced as broadly as claimed. The specification teaches analysis of 10 male subjects (8 Caucasian and two Hispanics). As illustrates in Figure 6, the level of dopamine is statistically different only in response to exercise at the peak time following the baseline measurement. At 30 minutes and 60 minutes the differences is not significant. Moreover, there is no indication of the 7R allele status of the various patients. There is no stratification of those ADHD patients with and without the 7R allele or those controls with the 7R allele. Thus, it is unclear how the 7R allele factors into the analysis. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are broadly drawn to any patient. The claims would encompass any ethnicity, any sex and adults and children. The art teaches that a study of children illustrated that girls and boys had different response to exercise (see Tantillo). Thus, within the subpopulation of children, boys and girls had different responses to exercise. The instant specification teaches the use of only boys. It is unpredictable whether girls would show the same responses. The instant specification samples boys from age 7-11 (see table 2). The specification further teaches that the alleles of the 7R varies between ethnic groups. The skilled artisan would be required to perform trial and error experimentation to practice the broad scope of the instant claims. The claims encompass any patient, children, adults, of any sex and ethnicity. The art teaches the unpredictability between these subgroups. Thus, it would constitute undue, unpredictable experimentation to practice the broad scope of the claims without further trial and error experimentation.

The claims are drawn to a method of testing for the presence of a marker within a block of linkage disequilibrium surrounding the DRD4 7R allele. The specification teaches DRD4 7R haplotypes and three markers surrounding the 7R allele which are not in complete linkage disequilibrium. The specification fails to provide any guidance of additional markers. Wang teaches 70 SNPs have been found, only a fraction which are linked to 7R. It would require unpredictable trial and error experimentation to determine which alleles identified are in linkage disequilibrium and surrounding the 7R allele. The art, namely Meyer, teaches SNPs within the same gene, in the same block are not associated with the same diseases. Specifically Bhaduri teaches that the 12bp duplication which is in LD with the 48bp VNTR is not associated with ADHD. Thus, the

skilled artisan would be unable to assume that any SNPs or variant located in proximity to the 7R alleles would be in linkage disequilibrium and encompassed within the scope of the claims.

The claims are drawn to evaluating "the level of dopamine" but fails to provide any context of level of dopamine. The specification illustrates dopamine levels on a scale of 5-25, but fails to provide any guidance which levels are indicative of ADHD and normal individuals. Inter-individual variation would be expected. Moreover, the specification illustrates that the only statistically significant difference occurred at peak exercise and not at 30 or 60 minutes following exercise. Thus, the evaluation of dopamine levels would have been unpredictable at the points after peak evaluation. Moreover, there is no indication of the 7R allele status of the various patients. There is not stratification of those ADHD patients with and without the 7R allele or those controls with the 7R allele. Thus, it is unclear how the 7R allele factors into the analysis.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the claims broadly encompass subject matter that is not enabled in the art and specification. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized difficulties of associating alleles with phenotypes without further

unpredictable and undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to Arguments

The response traverses the rejection. The response asserts the claims are enabled according to the Wands factors. The applicant correctly identifies the issue as to whether the test for genetic polymorphisms in DRD4 and dopamine release are associated with ADHD and how.

The response argues Tantillo provides no evidence that girls with ADHD will fail to exhibit the effects observed in boys with respect to dopamine release in response to a stimulus. This argument has been reviewed but is deemed not persuasive. First, the claims encompass all humans, adults and children and the specification only analyses boys. Tantillo supports the position that girls and boys respond differently to various test parameters such as rate of spontaneous eye blinks, acoustic startle eye blink response, and motor impersistence. Since the art teaches that girls and boys respond differently to various parameters, it is unpredictable how a level of dopamine release would be standard across all genders and ages. The instant specification only appears to analyze 7-10 yr old males. This is not representative of the girls and

additional ages given the teachings in the art of differences. The response, on page 8, states that applicants disclosure is enabling for a sufficient portion of the genus (males, approximately 50 % of the genus). This argument has been reviewed, but deemed not persuasive. The genus which the specification may have enabled would be limited to boys. This is not representative of adult women or men and girls. Moreover, even if the teachings were representative of all males, the scope of the claim is not commensurate with only males.

The response asserts that Bhaduri's findings with respect to a lack of association between ADHD and the exon 1 1q2 bp duplication are merely preliminary. This argument has been reviewed. While Bhaduri teaches that the marker is in high LD, as similarly found in the instant case, with the 7R allele, Bhaduri raises the unpredictability of an association with ADHD despite the high LD.

The response asserts that the issues raised by Hirschhorn were addressed by the present invention. The response asserts that the samples were broadly selected and did not display population stratifications. This argument has been reviewed but is not convincing. The specification analyzes 10 patients, namely 8 Caucasians and 2 Hispanic, were analyzed. This is not a large sample across a representative ethnic group. The study of 600 chromosomes appears to be an attempt by the inventors to find additional markers and catalog them into haplotypes. This is no indication that these haplotypes are associated with ADHD status.

Next the response asserts Meyer is irrelevant because the invention exploits the principle that a single SNP in a gene indicates that all SNPs in the gene are associated

with the disease. This argument has been reviewed but is not persuasive. The instant invention fails to show that the SNPs and markers in LD are associated with LD. The specification only states the SNPs and makers are in LD. Both Meyer and Bhaduri raise the issue of enablement for markers that are in LD without any association studies.

The response focuses on the association of 7R allele with ADHD. The claim requires analysis of both markers surrounding 7R allele and evaluating the level of dopamine. However neither the specification, nor the art appear to provide any guidance how to relate the results to ADHD. Would the absence of the marker but the presence of statistically high levels of dopamine indicate ADHD? Or the absence of the marker but the presence of low levels of dopamine? There is no guidance how to make the analysis. Similarly, there is no level of dopamine or stimulus provided. The response provides some indications of the patient's ADHD status such as normal dopamine release in children but also have the 7R allele are likely to "grow out" of many of the ADHD symptoms. Moreover, the response states that "a diagnosis of DRD4 7R in a child displaying ADHD symptoms without cognitive deficits and without a dopamine release abnormality may actually be a positive finding, as many such patients that do not display cognitive deficits can become more productive with maturity." These correlations and indications do not appear to be in the specification or the claims. It is unpredictable based upon the specification, claims and art at the time the invention was made how the skilled artisan would provide an indication of the patient's ADHD status based upon the method provided.

The claims are drawn to testing a patient for ADHD status by testing for a marker in LD with DRD4 7R allele and evaluating the level of dopamine release. There is no guidance in the specification how the skilled artisan would take the information obtained from these two experiments and provide an ADHD status. The specification does not provide any working examples where a marker in LD with DRD4 7R allele and dopamine levels are analyzed to provide ADHD status.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

B) Claim 1 requires testing for ADHD status, however the claims fail to provide how to test for the status. For example, if the results indicate that the L2 allele is present and the dopamine level is 20pg/ml, what the patient ADHD status was. Therefore, the claims are unclear how to test for ADHD status.

Response to Arguments

The response traverses the rejection. The response asserts the rationale for determining ADHD status is set forth throughout the specification and particularly on

page 4. The response states that the specification teaches that the absence of an increase in dopamine release in response to a stimulus is indicative of ADHD status. This argument has been considered but is not convincing because the specification does not clearly set forth the indication of the patient's ADHD status in at least one situation. Moreover, the specification does not appear to provide any threshold dopamine level to judge whether the dopamine level is (+) or (-).

For example, it is presumed that a patient (+) for the polymorphism and (-) for change in DA would be patients that could be identified as (+) for ADHD.

It is also presumed that a patient (-) for the polymorphism and (+) for change in DA would be patients that could be identified as (-) for ADHD since they do not possess the polymorphism and have dopamine changes associated with normal activity.

The specification appears to discuss patients who are (+) for the polymorphism and (+) for change in DA as patients who result in "false positive" diagnosis of ADHD since they do not have cognitive defects associated with ADHD (para 169). These patients would thus be identified as negative for ADHD.

The specification however fails to provide any guidance if the patient is (-) for the polymorphism and (-) for change in DA. The skilled artisan would be unable to provide any status for these patients.

It is noted that the claims are not drawn to determining the status for only individuals that tested positive for the 7R allele, as indicated by the presence of one or more of the recited polymorphisms.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

11. No claims allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz, can be reached on (571)272-0763.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
September 25, 2009